

REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and following arguments is respectfully requested.

Claims 21-37 are pending. Claims 35 and 36 are withdrawn. Claims 21-34 and 37 are under consideration. Claims 21 and 25 have been amended as explained below. No new matter has been added as a result of these amendments.

Claim Objection

Claim 25 is objected to because "in one of the claim 21" is grammatically incorrect. Applicant has corrected this grammatical error by deleting "one of the" from claim 25. Withdrawal of the objection to claim 25 for this informality is respectfully requested.

Rejection of Claims 21-34 Under 35 U.S.C. § 112, Second Paragraph

Claims 21-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner states that the recitation "cannot bind to the matrix" in steps ab) and bb) of claim 21 is unclear as to whether any structural limitations are being imposed on the oligonucleotide that causes its inability to bind to the matrix.

Applicant respectfully traverses this rejection. Applicant's arguments in the previous Amendment are incorporated herein.

The Examiner rebuts Applicant's arguments by stating that it is unclear what Applicant intends to limit the claim to since it is not clear how the oligonucleotide cannot bind to the matrix. The Examiner suggests amending the

claim to recite a specific structure the oligonucleotide has that disallows it from binding to the matrix.

The specification on page 10, lines 1-13, states:

"One of the two oligonucleotides that are to be linked in each reaction step (the so-called anchor oligonucleotide) can be coupled to a solid matrix by means of a modification e.g. a low molecular chemical compound such as biotin or digoxigenin. In a preferred embodiment these are magnetic streptavidin-coated or anti-digoxigenin-coated beads. The other oligonucleotide (the so-called splinker oligonucleotide) also has a blocked end but does not have such a modification or has another type of modification. The important point is that the anchor oligonucleotides can be separated from the splinker oligonucleotides by binding to the suitable matrix. Hence any compounds e.g. biotin, digoxigenin, fluorescein isothiocyanate (FITC), amino compounds, succinyl esters and other compounds familiar to a person skilled in the art can be used provided they are suitable for mediating a direct or indirect (e.g. by means of an antibody) binding to a solid phase."

Applicant submits that this passage clearly describes how the oligonucleotide recited in steps ab) and bb) cannot bind to the matrix. For example, a variety of compounds are absent from the oligonucleotide. These compounds are familiar to a person skilled in the art. Examples of such compounds are biotin, digoxigenin, fluorescein isothiocyanate (FITC), amino compounds and succinyl esters that may be incorporated into the oligonucleotide and that mediate the binding of the oligonucleotide to the solid phase. Other methods of preventing binding to the matrix that are known in the art and consistent with the method of the present invention may be used.

For these reasons, Applicant respectfully requests withdrawal of the rejection of claims 21-34 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 21-27, 29-32, 34 and 37 Under 35 U.S.C. § 103(a)

Claims 21-27, 29-32, 34 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.*, U.S. Patent No. 5,888,737 (herein "DuBridge") in view of Church *et al.*, U.S. Patent No. 6,485,944 (herein "Church").

The Examiner maintains the rejection made in the previous Office Action. Applicant respectfully traverses the rejection. Applicant's arguments in the previous Amendment are incorporated herein.

The Examiner makes several remarks which Applicant wishes to address herein.

First, the Examiner states that Applicant argues that the steps of washing away the shorter oligonucleotide are not recited in claim 21 and therefore these steps are irrelevant. Applicant would like to respectfully point out to the Examiner that these steps are recited in claim 21 as follows.

Step ad) recites "removing oligonucleotides from steps aa), ab) and ac) that are not coupled or ligated (emphasis added)." Step ae) further recites "cleaving the ligation product from step ac) ...and resulting in an elongated oligonucleotide and a shorter oligonucleotide (emphasis added)." Step af) further recites "separating ... the shorter oligonucleotide from the elongated oligonucleotide from the elongated oligonucleotide obtained in step ae) (emphasis added)." Step ag) recites "repeating steps ab) to af) at least once." Steps bd), be) and bf) recite similar steps as steps ad), ae) and af) as indicated above. Step bg) further recites "repeating steps bb) to bf) at least once ... removing oligonucleotides that are not coupled or ligated to obtain a ligation product (emphasis added)." Finally, step e) recites "cleaving the ligation product ... and resulting in an elongated oligonucleotide and a shorter oligonucleotide (emphasis added)" and step f) recites "separating the type IIS restriction enzyme and shorter oligonucleotide from the elongated oligonucleotide obtained from step e) (emphasis added)."

Applicant submits that it is clear from these steps that the shorter oligonucleotides are removed while the longer oligonucleotides are retained in the claimed method.

As stated in Applicant's previous Amendment, DuBridge discloses a method for analyzing terminal nucleotides of polynucleotides by specific ligation of labeled adaptors (column 1, lines 4-7). DuBridge's Figure 2A illustrates a method for determining the identity of the nucleotides at the terminus of a polynucleotide (column 2, line 50 to column 3, line 8) and does not retain the longer oligonucleotide while removing the shorter oligonucleotide. Likewise, DuBridge's Figures 3A to 3E all clearly show, in a series of steps, the shortening of oligonucleotides that are being identified.

Second, the Examiner refers Applicant to DuBridge's Figure 2B and states that DuBridge discloses producing both a shorter oligonucleotide (the oligonucleotide on the left) and a longer oligonucleotide (the oligonucleotide on the right). However, DuBridge does not retain the longer oligonucleotide while removing the shorter oligonucleotide. The last two steps depicted in Figure 2B show that the longer oligonucleotide (the oligonucleotide on the right) is removed (indicated by the term "wash") and the shorter oligonucleotide (the oligonucleotide on the left) is retained.

In an effort to expedite prosecution of the instant application, Applicant has amended step f) in claim 21 to recite "separating and removing the type IIS restriction enzyme and shorter oligonucleotide from the elongated oligonucleotide obtained from step e), wherein the elongated oligonucleotide is retained (emphasis added)." Support for this amendment is indicated above and can be found amply within the specification, for example in Figures 1 and 14. Applicant submits that it is clear that claim 21 contains the limitation of retaining an elongated oligonucleotide.

Finally, the Examiner states that DuBridge does not disclose step bg) of claim 21, wherein the oligonucleotide linked to the solid support is cleaved using type IIS restriction enzymes. The Examiner provides Church as teaching this limitation. However, Applicant submits that Church does not cure the deficiencies of DuBridge as stated above.

Additionally, Applicants respectfully would like to point out the following deficiencies of the DuBridge disclosure with respect to the claimed method.

First, as recited in steps aa) and ab) of claim 21, each of the oligonucleotides contains a recognition sequence for a type IIS restriction enzyme, whereby the recognition sequences are different in each of the two oligonucleotides. This is a prerequisite for the proper functioning of the claimed method. Specifically, once several nucleotides are added on one side of the first oligonucleotide, the resulting elongated first oligonucleotide has to be cut by a type IIS restriction enzyme specific for the second oligonucleotide. Additionally, after several repetitions of such additions reactions, the resulting, several-times-elongated oligonucleotide has to be cut by the type IIS restriction enzyme specific for the first oligonucleotide. Therefore, there is a need for a sequence of ligation and cleavage, and a need for two different type IIS restriction enzymes in the two oligonucleotides to be ligated.

In contrast, DuBridge does not disclose or suggest that each of a first and a second oligonucleotide comprise a recognition sequence for a type IIS restriction enzyme as evidenced by the following passages in DuBridge's disclosure:

- 1) Column 11, lines 28-37 only refers to the use of type IIS restriction endonucleases but does not specifically state in which molecule a respective recognition site is contained,
- 2) Column 6, lines 4-5 specifies that the double stranded adapter has a nuclease recognition site for a type IIS restriction enzyme,
- 3) Column 12, lines 65-67 specifies that in the ligation product consisting of the target polynucleotides and cleavage adapter, the cleavage occurs by the recognition site provided by the cleavage adapter,
- 4) Column 17, lines 37-40 confirms that a cleavage is only possible upon complex formation of the target nucleic acid and the adapter molecule, and
- 5) Figures 2A and 2B indicate that the recognition site of the type IIS restriction enzyme (as a hatched bar) is provided only by the adapter molecule.

Additionally, column 10, lines 25-26 of DuBridge states that “cycles of ligation may be used, but are not required (emphasis added)”. This is contrary to the claimed method.

Finally, as briefly pointed out above, DuBridge’s method is directed to providing sequence information rather than ligation or making an elongated oligonucleotide. Accordingly, the target nucleic acid is truncated by several rounds of adapters ligated to the target nucleic acid and subsequently cut off from the ligation product by the type IIS restriction enzyme. However, DuBridge does not disclose or suggest combining the adapter molecules to form a larger nucleic acid molecule.

Church is deficient in that it does not disclose or suggest that the first and a second oligonucleotide each comprise a different recognition sequence for a type IIS restriction enzyme. By combining the DuBridge reference with the Church reference without any other teachings that employ a first and a second oligonucleotide that each comprises a recognition sequence for a type IIS restriction enzyme in order to arrive at the claimed method is impermissible hindsight.

For all of the above reasons, Applicant respectfully requests withdrawal of the rejection of claims 21-27, 29-32, 34 and 37 under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.*, U.S. Patent No. 5,888,737 in view of Church *et al.*, U.S. Patent No. 6,485,944.

Claim 28 is rejected under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.*, U.S. Patent No. 5,888,737 (herein “DuBridge”) in view of Church *et al.*, U.S. Patent No. 6,485,944 (herein “Church”) as applied to claim 21, and further in view of Lane *et al.*, U.S. Patent No. 5,770,365 (herein “Lane”).

The Examiner cites Lane as teaching the modification of the oligonucleotide of step aa), ba) or a) via coupling a loop region to the solid matrix. However, Lane does not cure the deficiencies of DuBridge and Church as stated above. Applicant’s arguments above are incorporated herein.

Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 28 under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.*, U.S. Patent No. 5,888,737 in view of Church *et al.*, U.S. Patent No. 6,485,944, and further in view of Lane *et al.*, U.S. Patent No. 5,770,365.

Claim 33 is rejected under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.*, U.S. Patent No. 5,888,737 (herein "DuBridge") in view of Church *et al.*, U.S. Patent No. 6,485,944 (herein "Church") as applied to claim 21, and further in view of Israel, U.S. Patent No. 5,981,190.

The Examiner cites Israel as a teaching using ribozymes instead of type IIS restriction enzymes. However, Israel does not cure the deficiencies of DuBridge and Church as stated above. Applicant's arguments above are incorporated herein.

Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 33 under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.*, U.S. Patent No. 5,888,737 in view of Church *et al.*, U.S. Patent No. 6,485,944, and further in view of Israel, U.S. Patent No. 5,981,190.

CONCLUSION

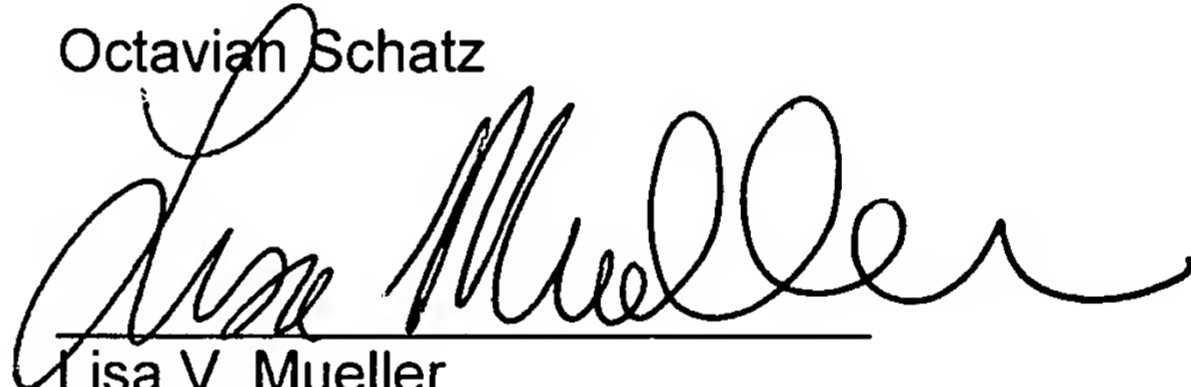
Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. Sections 112 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,

Octavian Schatz

A handwritten signature in black ink, appearing to read "Lisa V. Mueller", written over a horizontal line.

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